Clinical Aspects of Liver Diseases

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The 2000 edition of the pharmacopoeia („Rote Liste“) issued by the Association of the German Pharmaceutical Industry comprises 7,355 chemically defined preparations, 1,239 plant-based remedies, 423 organ-based preparations and 667 homoeopathic pharmacons. The total of 9,684 pharmaceutical preparations contains approximately 2,900 medically effective substances. Of the 11,714 administration forms (1996), a total of 854 (7.3%) have an alcohol content of up to 80 volume percent and more. (s. p. 51) The number of proprietary drugs available on the German market, but not listed in the above-mentioned pharmacopoeia, is enormous; it has been estimated to exceed 1,000 preparations. • All in all, a total of approximately 12,000 proprietary drugs are available on the German pharmaceutical market today.

1 Medicaments as foreign substances

Xenobiotics: Xenobiotics are defined as exogenously administered or endogenously produced foreign substances that impair and ultimately damage the ecology and homeostasis of cellular systems. The definition also includes medicinal preparations. (s. pp 43, 44)

All orally or parenterally administered drugs normally enter the liver and from here, after passing through biotransformation systems, are released into the cardiovascular system either in an unconverted or in a metabolically converted state. In addition, systemic effects always have to be anticipated in cases of topical administration (cutaneous, inhalant). • Metabolic processes generate metabolites, more specifically catabolites (= degradation products) and anabolites (= synthesis products). These biochemical processes are catalyzed or controlled inside and outside the cell by enzymes, hormones and the neurovegetative system. • Exogenous substances, however, may also be metabolized and excreted without enzymatic processes by spontaneous chemical conversion (= metabolonates).

► Of the many xenobiotics and medicaments, only a small fraction are sufficiently water-soluble to be excreted in an unchanged state via the kidneys or the bile. These are strongly polar groups such as penicillin, cephalosporin, tetracycline, thiazide, amiloride and cromoglycic acid; so far, no metabolites of these substances have been found. • The mainly lipophilic foreign substances or medicaments can only be eliminated by biotransformation, i.e. by the metabolic production of water-soluble compounds. The metabolism of drugs via the kidneys, intestinal mucosa, muscles, lungs and skin is of minor importance in this context. (s. pp 44, 45) Biotosomometabolites (or biotosomometonates) may occur as a result of faulty biochemical reactions. (s. p. 46) (s. fig. 3.8) • The metabolism of medications also involves antioxidants (s. p. 56) as well as the functions of the hepatic RES. (s. p. 55) • The biochemical mechanisms related to the metabolism of xenobiotics may be affected by unalterable factors such as genetics, gender and age, or by variable factors such as the protein content of food, alcohol and tobacco smoke. In individual cases, such factors may be of crucial importance. (s. tab. 3.18) (s. fig. 3.8) • The variable effects and side-effects of medications are genetically determined, i.e. the pharmaco-kinetic characteristics of a certain drug may be largely determined by the pharmacogenetics of the individual patient. (8, 23, 27, 55, 77)

The recognition that a system which metabolizes drug products can likewise produce highly reactive toxic metabolites proved crucial. As the liver has the highest content of enzyme biotransformation systems, it is the main site of production of such reactive metabolites and is thus more susceptible to damage. • Medicaments must therefore be regarded as potentially hepatotoxic substances. Basically, they can trigger a vast range of functional and morphological changes in the liver. The resulting hepatic damage can mimic almost any acute or chronic liver disease. This means that in terms of function, morphology and clinical presentation, it is virtually impossible to differentiate between drug-induced liver diseases and the non-iatrogenic liver diseases they mimic.

Drugs always have to be considered in the differential diagnosis of any case of liver disease lacking unequivocal clarification. The diagnosis of a pharmacological-induced liver disease depends on the reliable exclusion of other potential causes of the existing disease as well as on the so-called withdrawal trial.

2 Frequency

Quantification: With regard to their frequency, adverse side-effects are classified as (1.) frequent (>10%), (2.) occasional (1–10%), (3.) rare (<1%), (4.) very rare (<0.1%), and (5.) isolated cases (not yet quantifiable).

Surprisingly – but also understandably, given the great difficulties related to any reliable quantification – only very little information exists about the frequency of adverse side-effects in patients taking medication. A total of 2.3% or 1.9–6.2%, sometimes even up to 20%, of all hospitalizations has been attributed to medication-related diseases; 2–5% of all hospitalized types of jaundice and 25% of all patients with acute necrotizing hepatitis have been diagnosed as medication-induced toxicosis. A ten-year study carried out in Sweden between 1966 and 1975 listed 274 deaths due to pharmaceutical preparations, 23 (9%) of them with toxic liver damage. (10, 11, 29, 59, 60, 64, 100)

► A comprehensive survey carried out in 1988 in a total of 2,008 medical practices in Germany found drug toxicity in 12.4% of the 7,095 patients suffering from liver disease (50): on average, the patients had been taking medication for approximately four years, with a max-
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The maximum period of regular intake of up to 30 years (!). In 32.4% of patients, the liver had been exposed to a “double burden” as a result of the concomitant and regular daily ingestion of alcohol. This finding is of remarkable practical relevance. • In 1989 we conducted a renewed survey in an additional 2,990 medical practices (2,650 in Germany and 340 in Austria) and found that 17.7% of cases of acute liver disease in Germany and 14.3% of cases in Austria had been caused by drug toxicity, while 25.1% of cases of chronic hepatic disease in Germany and 22.1% of cases in Austria were attributable to the intake of medicaments. (51)

3 Pathogenesis

Foreign substances, including medicinal products, are classified as obligate (directly effective) or as facultative (indirectly effective) hepatotoxins, depending on their degree of hepatic toxicity. Hepatotoxins are therefore grouped as either directly toxic or indirectly toxic according to the pathogenetic mechanisms of liver damage. Indirect hepatotoxins may, however, also cause an idiosyncratic type of liver impairment through immunological or metabolic mechanisms. (10, 22, 44, 49, 52, 54, 56, 59, 64, 72, 83, 88, 100) (s. tab. 29.1) (s. fig. 29.1)

3.1 Obligate hepatotoxins

Direct hepatotoxins cause liver damage in all exposed persons (i.e. it is always predictable). They cause toxic damage. This direct toxic response manifests either because the hepatotoxic foreign substance cannot be detoxified at all or because detoxification by biotransformation does not proceed rapidly enough. Following a relatively short and usually stable latent period, the hepatotoxin directly effects the destruction of cellular structures, e.g. by inactivating enzymes of the intermediary metabolism, by denaturation of cellular proteins or by lipid peroxidation. (s. fig. 21.8) This leads to fatty infiltration or necrosis of the liver cells. Obligate hepatotoxic medicaments are rarely clinically tested, since their hepatic toxicity is normally recognized at an early stage during animal experiments. However, a negative animal result alone is not enough to ensure safety in this respect. This has been demonstrated in the case of the preparations benoxaprofen and ticrynafen, in which the respective hepatic toxicity was only recognized after they had been administered to “thousands of patients”. (56) Obligate hepatotoxic pharmacons are only likely to be tested clinically if their therapeutic benefit substantially outweighs their hepatic toxicity (e.g. as an effective cytostatic agent). • Some medicaments that had proved to be non-hepatotoxic may, however, become obligate (directly) hepatotoxic substances in overdoses (= intoxication), as is the case with isoniazid, mercaptopurine, methotrexate, paracetamol, tetracycline, etc.

3.2 Facultative hepatotoxins

In contrast, indirect hepatotoxins only cause liver damage in a small number of exposed persons (i.e. it is not predictable). There is an individual, situation-related propensity towards the biotransformational production of indirect hepatotoxins or a manifestation of individual hypersensitivity (= idiosyncrasy). • Indirect toxic hepatic damage results from an interference of foreign substance metabolites (which are, strictly speaking, biotoxometabolites) with specific reactions of the intermediary metabolism. Such primary metabolic disorders include, for example, the alkylation or acylation of proteins, a lack of ATP or UTP, the blocking of receptors as well as of SH groups, or the binding to nucleoproteins. Only at a subsequent stage do these disorders result in structural damage: steatosis or necrosis of liver cells, chole-

Criteria: Hepatotoxic xenobiotics:

- obligate (= direct)
- facultative (= indirect)

Liver damage:

- directly toxic
- indirectly toxic
- idiosyncratic
  - immunological
  - metabolic

| 1. Predictable toxicity | + |
| 2. Latent period | short, relatively stable |
| 3. Dose dependency | + |
| 4. Reproducibility | + |
| 5. Evidence from animal experiments | |

Tab. 29.1: Pathogenetic criteria of hepatotoxic xenobiotics and the basic types of liver damage induced by foreign substances (modified in accordance with 10, 44, 57, 59, 83, 88)
stasis and also tumour formation. This type of impairment displays the features of facultative hepatotoxins. • Idiosyncratic liver damage is caused by facultative hepatotoxins. It only occurs in persons with a specific hypersensitivity to the ingested foreign substance or to one of its metabolites. Idiosyncratic liver damage may take an immunological or a metabolic course.

In the immunological type of hepatotoxicity, the foreign substance or one of its metabolites is bound to a liver cell protein. This leads to the production of a hapten (antigen), which in turn triggers a humoral or cell-mediated immune reaction and helps to detect autoantibodies, especially LKM-2 and LKM-3. (s. p. 615) The immunological type of liver damage is often accompanied by allergic symptoms (e.g. fever, exanthema, pruritus, eosinophilia) and by correspondingly identifiable histological findings (granulomas, eosinophilic infiltrations). • The metabolic type is reflected in an abnormal metabolic reaction, which occurs in a small number of exposed persons who are highly sensitive to the xenobiotic or to one of its metabolites. In general, this abnormal type of metabolism is genetically determined. It results in the production of biotoxometabolites. This mechanism is thought to come into play with isoniazid and iproniazid, for example. Symptoms of cholestasis are present, and there is often AMA-M6 positivity. (40)

However, these two types of damage resulting from facultative hepatotoxins do not explain all pathological metabolic effects, such as the occasional occurrence of allergens, mutagens, procarcinogens, and “new” toxins. (s. fig. 3.8) In this context, 2 hypotheses are conceivable: on the one hand, these pathological “end products” may occur in combined toxic/idiosyncratic liver impairment and on the other hand, the “end products” may develop as a result of biotoxometabolites binding to specific cellular proteins, sometimes to “altered” cellular proteins after the occurrence of toxic liver damage.

4 Morphological reactions

4.1 Adaptive changes

The xenobiotic-related induction of the biotransformation system usually leads to an initial adaptive response: hyperplasia of the SER (= smooth endoplasmic reticulum) occurs. (s. pp 352, 474) (s. fig. 21.2) The cytoplasm takes on the turbid appearance of opalescent glass. These ground glass hepatocytes (s. pp 101, 353) (s. figs. 5.7; 22.7) are not produced by all foreign substances, but they may possibly be evident as an unspecific finding in chronic hepatitis B. The cytoplasm is fine-grained or fine-alveolate and looks pallidly eosinophilic. The nucleus, as well as the rough endoplasmic reticulum, move to the clearly contoured cell membrane. Anisokaryosis and binuclear liver cells point to an accelerated cell metabolism. In addition, giant mitochondria may also be present. (s. fig. 28.2) (s. pp 355, 475)

If a sufficient level of adaptation cannot be achieved, regressive alterations occur; homogeneous cytoplasm droplets are produced, which are then transformed into pigment granules of the lipofuscin type. It is a characteristic of lipofuscinosis that, after the xenobiologically induced adaptation of the smooth reticulum (s. p. 353) (s. fig. 21.3), it appears in enlarged, hypertrophied liver cells – unlike lipofuscinosis in brown atrophy. • There is no sharp distinction between adaptive and alternative hepatic changes. Single-cell necrosis may already be present in this border area, possibly activating the local stellate cell system. • There may be a vast range of morphological changes depending on the individual manifestation, the pathogenetic mechanisms and the administered dosage of a drug as well as the duration of its intake. (9, 20, 63)

4.2 Alterative changes

Alterations in the liver parenchyma as a result of foreign substances are characterized by several parenchymal, mesenchymal and vascular basic reactions as well as by benign or malignant neoplasia. It seems reasonable to
classify the morphological findings in accordance with the acuteness and chronicity of their occurrence—bearing in mind all fundamental and individual reservations with regard to their systematization. (s. tab. 29.2).

### Tab. 29.2: Xenobiotic-induced acute and chronic types of morphological liver damage (with fundamental and individual reservations) (s. tab. 29.9)

<table>
<thead>
<tr>
<th>Acute liver damage:</th>
<th>Chronic liver damage:</th>
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<tbody>
<tr>
<td>1. Parenchymal findings:</td>
<td>1. Parenchymal findings:</td>
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<tr>
<td>- Steatosis</td>
<td>- Chronic hepatitis</td>
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<tr>
<td>- Macrovesicular steatosis</td>
<td>- Cirrhosis</td>
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<tr>
<td>- Phospholipidosis</td>
<td>- Primary biliary cholangitis</td>
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<tr>
<td>2. Necrosis</td>
<td>2. Inflammatory reactions:</td>
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<tr>
<td>- Perivenous</td>
<td>- Granulomas</td>
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<td>- Focal</td>
<td>3. Vascular changes:</td>
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<tr>
<td>- Diffuse</td>
<td>- Veno-occlusive disease (VOD)</td>
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<td>- Group necroses</td>
<td>- Budd-Chiari syndrome</td>
</tr>
<tr>
<td>3. Cholestasis</td>
<td>4. Fibrosis</td>
</tr>
<tr>
<td>- Canalicular</td>
<td>5. Tumours:</td>
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<tr>
<td>- Hepatocanicular</td>
<td>- Adenomas</td>
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<tr>
<td>- Jaundice</td>
<td>- Adenoma</td>
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<tr>
<td>2. Vascular changes:</td>
<td>6. Combined forms</td>
</tr>
<tr>
<td>- Intimal hyperplasia</td>
<td>- Fibrosis</td>
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<tr>
<td>- Dilatation of sinusoids</td>
<td>- Jaundice</td>
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<tr>
<td>- Peloisis hepatis</td>
<td>- Cholestasis</td>
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<tr>
<td>- Portal vein thrombosis</td>
<td>- Cell ballooning</td>
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<tr>
<td>3. Inflammatory reactions:</td>
<td>- Necrosis</td>
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<td>- Infiltrations</td>
<td>- Jaundice</td>
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<td>4. Combined forms</td>
<td>5. Tumours:</td>
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<td></td>
<td>- Adenomas</td>
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<td>- Adenoma</td>
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<td>- Focal nodular hyperplasia</td>
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<td>6. Combined forms</td>
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<td>- Carcinomas</td>
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<td>- Hepatocellular</td>
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<td>- Cholangiolar</td>
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<td>- Sarcoma</td>
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<td>- Angiosarcoma</td>
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### 4.2.1 Steatosis

Microvesicular steatosis (s. p. 524) presents as deposits of tiny lipid particles in the cisterns of the endoplasmic reticulum. The lipid particles are thus surrounded by a membrane. The nucleus remains at the centre of the cell. • Macrovesicular steatosis (s. p. 523) often develops further into necrosis if the intake of a foreign substance is continued. (17) • Phospholipidosis is regarded as a special type of steatosis. The hepatocytes are enlarged and display a foamy cytoplasm resulting from a marked increase in phospholipids. Electron microscopy shows crystalline inclusions. This idiosyncratic hepatic lesion of the metabolic type has been observed for example during the administration of amiodarone. This substance has a long half-life and therefore remains in the liver for several months. Potentially fatal cirrhosis may occur. (s. p. 524)

### 4.2.2 Necrosis

Hepatocellular necrosis usually presents as coagulation necrosis. It is an aetologically unspecific event that can have various causes, but it constitutes the most significant type of xenobiotic-induced hepatic damage. Cellular necrosis may affect either single cells or cell groups. (s. p. 355) A relatively characteristic feature of drug-induced toxicity is group necroses that are usually perivenously localized, sometimes sector-like and accentuated, always clearly demarcated and often confluent. Idiosyncratic liver damage induced by halothane leads to necrosis affecting the entire liver lobule in a diffuse way. (s. fig. 29.2) • Cellular necrosis is often preceded by cell ballooning (s. p. 353), which may appear as (1.) toxic swelling of cells or (2.) cellular hydrodrops. The hydroptic cells are enlarged; they do not store any glycogen and look pallid. Cytoplasmic basophilia is reduced. The cisterns of the smooth endoplasmic reticulum are greatly enlarged as a result of fluid storage.

The hyperchromatic nucleus decays due to karyolysis, which culminates in cell death.

### 4.2.3 Cholestasis

Xenobiotic-induced cholestasis can be detected in 3 morphological types: (1.) intercellular in the form of biliary thrombi, which are found in the dilated canaliculi, with adjacent hepatic cells usually displaying pericanalicular condensation of the rough endoplasmic reticulum as well as frequent manifestation of cellular hydrops; (2.) intracellular in the form of bile droplets, which can be demonstrated as bile deposits of varying sizes or as small bile-imbibed protein particles—this type points to severe cell damage; (3.) mixed form of inter- and intracellular cholestasis. (s. p. 205) (s. figs. 13.1, 13.4; 29.3, 29.4) • Disturbances of bile acid excretion are often accompanied by feathery degeneration of hepatic cells. (3, 7, 25, 31, 33–35, 37, 53, 67, 69, 76, 79, 84, 85) (s. p. 212) (s. fig. 22.4)

### Jaundice

Hyperbilirubinaemia may be caused by medicament-induced haemolysis. This disorder is regarded as an undesired drug action rather than liver damage brought about by foreign substances, since the bilirubin metabolism of the hepatic cells is not affected. Differential diagnosis must first rule out this haemolytic aetiology. • Jaundice (icterus) may be ascribed to various causes. (s. p. 193) Laboratory examinations and light microscopy have shown that several medicaments can (initially) cause a specific jaundice type, which continues in this same form until it disappears completely. • If the effect of the substance and the course of the jaundice persist, this drug-induced disorder can lead to cholestasis and morphological changes. (21)
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Fig. 29.4: Pronounced bilirubinostasis and cholestasis as well as stellate cell cholestasis (s. arrow) following administration of thiamazole (s. tab. 29.9)

**In a study of our own, we were able to demonstrate thiamazole-induced jaundice (maximum serum bilirubin 8.2 mg/dl with constantly normal values of AP, LAP and transaminases) over a period of more than five months.** (s. fig. 29.4)

4.2.4 Inflammatory reactions

The pattern of damage is as follows: steatosis, necrosis and cholestasis. They occur either as defined individual phenomena or (more frequently) in combination. Depending on the severity and extent of these morphological findings, 2 forms of inflammatory reaction are possible: (1.) a mesenchymal reaction and (2.) cellular infiltration. • In the **mesenchymal reaction** (s. p. 354), the stellate cell system is activated; the stellate cells and the mononuclear phagocytosis system proliferate. **Stellate cell nodules** form. (s. fig. 22.2) This process spreads from the sinusoids at the site of the lesion to include neighbouring parenchymal cells. The reticular lattice fibre is damaged and sometimes even destroyed. • In a more massive lesion, the inflammatory process spreads to the portal zone; histiocytes, lymphocytes and particularly eosinophilic leucocytes lead to portal zone cellulations with oedematous dilations, in some cases subsequent to portal fibrosis (s. fig. 21.13), or to **cholangitis** of the PBC type (s. fig. 29.5) as well as of PSC (e.g. due to floxuridine). • The hepatic mesenchyma may also respond with the formation of **granulomas**. (12, 48) (s. p. 357) This may well be the only morphological reaction provoked by foreign substances, although the formation of granulomas can sometimes be accompanied by the phenomena of steatosis, necrosis or cholestasis. From the pathogenetic perspective, granulomas can be caused by direct toxic as well as idiosyncratic lesions. The formation of granulomas has been observed during the administration of numerous pharmacons. (s. fig. 29.6) (s. tab. 29.9) (s. p. 355) • **Cellular infiltration** may vary in its degree, depending on the extent of the parenchymal lesion as well as on the type and duration of the toxic effect. In this context, cell infiltrates consisting of leucocytes and lymphocytes can be found within the liver acinus and/or in the portal zone; in contrast, in immunological-allergic impairment mechanisms, it is primarily lymphocytic and eosinophilic-leucocytic infiltrations that become manifest. This cellular reaction is also reversible. A more severe inflammatory reaction corresponds to unspecific reactive hepatitis. (s. p. 342) (s. figs. 21.1; 29.7) (s. tab. 29.9)

**Fig. 29.5:** Slightly florid, destructive cholangitis resulting from an ACE inhibitor (HE stain) (s. tab. 29.9)

**Fig. 29.6:** Epithelioid cell granuloma resulting from sulphonyl urea therapy (s. tab. 29.9)

**Fig. 29.7:** Inflammatory hepatic impairment with monocellular necrosis following administration of carbamazepine (s. tab. 29.9)
**4.2.5 Vascular reactions**

Medicinal agents (such as contraceptives) may result in proliferations of the intima in the hepatic artery and its branches. In some cases, these arterial alterations were associated with thrombosis in the hepatic veins. (88) 

Pharmacons can trigger 3 types of damage to the sinusoids: (1.) dilation of the sinusoids (e.g. by contraceptives), (2.) perisinusoidal fibrosis (e.g. by azathioprine, vitamin A and cytostatic agents), and (3.) peliosis hepatis (e.g. by contraceptives, anabolic and androgenic steroids, azathioprine, chenodesoxycholic acid). (13, 26, 98) (s. p. 354) (s. fig. 21.5)

The hepatic veins may be affected by xenobiotic-induced occlusion resulting from thrombosis or from proliferation starting in the intima and subsequently producing (secondary) thrombosis. An occlusion of the large hepatic veins is called Budd-Chiari syndrome. There are 2 distinct types, the truncular and the radicular form, the latter corresponding to veno-occlusive disease. (s. p. 220) Contraceptives (J.A. Ecker et al., 1966) and cytostatic agents are held responsible. Women develop this type of hepatic disease more than twice as often as men. (s. fig. 29.8)

**4.2.6 Liver tumours**

**Benign tumours**

As regards the neoformation of benign tumours, distinction is made between nodular adenoma and focal nodular hyperplasia (FNH). Because there are several transitional types between these 2 forms, they are generally regarded as variants of the same basic type of tumour.

Fig. 29.8: Budd-Chiari syndrome as a result of oral contraceptives (s. tab. 29.9)

Occlusion of the small hepatic veins is called veno-occlusive disease (VOD) (G. Bras et al., 1954; K. L. Stuart et al., 1957). It is identical to the radicular type of the Budd-Chiari syndrome. (s. p. 220) Cytostatics and azathioprine are among the alleged causal agents. (98) The diagnosis is based on imaging techniques (ultrasound, CEDS, CT), and sometimes on liver biopsy. (s. fig. 29.9) (s. tab. 29.9) • (see chapter 39)

Fig. 29.9: Intima proliferation and thrombosis of a (radicular) hepatic vein resulting from Senecio alkaloids (s. tab. 29.9) (H.-W. Altmann, 1980). Both types may be multiple. (13, 24, 42, 94, 96) (s. tab. 29.9)

Adenoma: The potential association of hepatic adenoma with the long-term use of oral contraceptives was first suggested by I. K. Baum et al. in 1973. Although the detection of adenoma was extremely rare before 1954, more than 400 cases were published by 1985. This figure has probably risen even further, but such findings have seldom been published since that time, as the diagnosis was often deemed not worth reporting. Thanks to the ultrasound technique, which is now used on a routine basis, hepatocellular adenomas rarely escape detection today. Most of them are located close to the surface. (63) (We have data on some 8 unpublished cases.) (s. fig. 29.10)

Fig. 29.10: Adenoma (approximately 5 cm in diameter) following long-term use of oral contraceptives (s. tab. 29.9)

Focal nodular hyperplasia: FNH is regarded as the most common benign hepatic neoplasia. As is the case with adenoma, it may develop after the patient has taken oestrogens for a longer period (usually more than 4 or 5 years). In some cases, the lesion develops within 6 to
12 months after beginning the intake. (92) When the oral contraceptives are discontinued, the tumour regresses or disappears (completely). The frequency of oestrogen-induced hepatocellular adenoma and of FNH was considerably reduced after the introduction of low-dose oral contraceptives. A genetic predisposition is assumed on the basis of frequency within families. The liver-damaging effect seems to be closely connected to the C₁₈ and C₁₉ steroid ring and alkylation in the 17α-position. Even the simultaneous occurrence of an adenoma and FNH under oestrogen administration has been described. (23) While there is a clear connection between adenoma formation and the intake of oestrogens, the association between FNH and oestrogens, albeit plausible, still lacks confirmation. • However, our own observations strongly suggest a causal relationship. (s. fig. 29.11, 29.12) FNH may also be caused by azathioprine, clofibrate and nitrofurantoin.

![Fig. 29.11: Focal nodular hyperplasia in the left liver lobe following 7 years’ use of oestrogen](image1)

![Fig. 29.12: Focal nodular hyperplasia (same patient as in fig. 29.11) with parenchymal nodes between fibroses resembling portal zones](image2)

Diagnosis

Benign hepatic tumours triggered by medicaments are generally diagnosed at a late stage or coincidentally during abdominal sonography. The tumour develops asymptptomatically over an extended period of time. • Complaints only occur when the tumour has grown to a certain size: upper abdominal pressure and occasional pain radiating to the back or to the right shoulder. This may point to tumoural bleeding, the formation of subcapsular haematoma or impending rupture. A rupture is accompanied by the signs of acute abdomen and the symptoms of haemorrhagic shock (possibly with simultaneous abdominal trauma, straining or retching). • Diagnosis is possible by ultrasound and other imaging techniques (if necessary, with contrast medium). Laparoscopy also provides a reliable diagnosis. If at all, biopsy is only indicated by laparoscopy and using fine needle or Robbers forceps (there is a possible danger of bleeding due to the high degree of vascularization). • Values beyond the normal laboratory parameters (bilirubin, AP, GPT, cholinesterase, etc.) only occur once the tumour has reached a certain size. We have found subnormal or very low γ-GT values in almost all women taking oestrogen. Increased γ-GT values were accompanied by the onset of cholestasis. • (see chapter 36)

Malignant tumours

Evidence that focal nodular hyperplasia tends to degenerate into malignant tumours is still lacking. • Hepatocellular adenomas pose the (rare) risk of developing into hepatocellular carcinoma (M. Davis et al., 1975). Several cases have been published in recent years. (6, 38, 71, 89, 90) We can add our own observation here:

► A 60-year-old female patient was referred to us for differential diagnosis of cholestasis after having taken oestrogen for about 21 years (substitution following bilateral removal of polycystic ovaries): AP 206 U/l, LAP 52 U/l, γ-GT 7 U/l (!), GPT 42 U/l, GOT 32 U/l, GDH 12 U/l, copper 192 µg/dl, cholinesterase 2,150 U/l. Repeated measurements consistently provided normal values for α₁-fetoprotein; haemogram, LDH, iron, etc. were normal; demonstration of adenoma by ultrasound and CT with,
However, additional “unclear structures.” Laparoscopy confirmed the adenoma, together with several subcapsular bleeding foci and hepatocellular carcinoma (identified by forceps biopsy). (s. fig. 29.13)

In contrast to primary hepatocellular carcinoma, the α1-fetoprotein values are normal (G. Klatskin, 1977), which is also true of the case we presented above. In opposition to this, a rapid increase and significant rise in AFP values have been reported. (24) Metastasis is rare, and if so, relatively late. • It has been observed that hepatocellular carcinoma can follow the intake of hormone-based contraceptives as well as long-term administration (several years) of 17α-alkylated androgenic, anabolic steroids and methotrexate. Cholangiocarcinoma may also be caused by the long-term intake (several years) of hormone-based contraceptives, androgenic agents and α-methylidopa. The formation of angiosarcoma has likewise been attributed to the long-term use of oral contraceptives, oestrogens, androgenic and anabolic drugs. (s. tab. 29.9)

**Diagnosis:** Malignant tumour formation is accompanied by loss of appetite and weight, pain in the upper right abdominal quadrant, fever, specific laboratory findings and paraneoplastic symptoms. • (see chapter 37)

### 4.2.7 Fulminant liver failure

Fulminant or protracted liver failure is caused by medicaments in 10–15% of cases. A reduction in the functional liver mass to <20–35% is deemed to be a critical stage. However, the death of the patient may already occur due to secondary metabolic disorders (so-called exogenous hepatic coma) before the extent of the parenchymal loss has fallen below the critical threshold (so-called endogenous hepatocellular disintegration coma). (s. tab. 29.9)

**Three forms** of drug-induced liver failure are distinguished: (1.) obligate, dose-dependent toxicity (e.g. paracetamol), (2.) unpredictable, idiosyncratic liver insufficiency (e.g. isoniazid), and (3.) immunoallergic idiosyncrasy (e.g. halothane, carbamazepine, phenytoin). (5, 14, 15, 39, 41, 53, 61, 68, 70, 78, 99)

Initially, unspecific complaints may include nausea, inappetence and fatigue. • In some patients, idiosyncratic hepatocellular damage may be accompanied by hypersensitive reactions (e.g. fever, exanthema, eosinophilia, lymphocytosis, arthralgia).

Obligate, dose-dependent medicament-induced toxicity need not be feared, since substances which predictably cause severe toxicity are not usually applied as medical remedies. It is only in cases where the therapeutic effect clearly outweighs the known type of damage that an obligate toxic substance is administered as a therapeutic agent – but in accordance with strict criteria!

It follows that almost all cases of fulminant or protracted liver failure caused by a certain substance are isolated occurrences that cannot be foreseen. Despite correct dosage and observance of all possible interactions, they develop as a result of individual idiosyncrasy. (s. tab. 29.3)

<table>
<thead>
<tr>
<th>Acarbose</th>
<th>Labetalol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>Leflunomid</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Lisinopril</td>
</tr>
<tr>
<td>Amphetamine  B</td>
<td>MAO inhibitor</td>
</tr>
<tr>
<td>Antirheumatics</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Benoxaprofen</td>
<td>Methylxanthine</td>
</tr>
<tr>
<td>Bromfenac</td>
<td>Minocycline</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Nefadodone</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Niacin</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>Nibutamid</td>
</tr>
<tr>
<td>Cyproterone</td>
<td>Nimesulide</td>
</tr>
<tr>
<td>Cytostatics</td>
<td>Niperotidin</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Dicoumarol</td>
<td>Ofloxacin</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Dideoxyinosine</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Pemoline</td>
</tr>
<tr>
<td>Ebrotidine</td>
<td>Phenhydrazine</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>Phenprocoumon</td>
</tr>
<tr>
<td>Enflurane</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Etosside</td>
<td>Pirprofen</td>
</tr>
<tr>
<td>Exiön</td>
<td>Prophylthion</td>
</tr>
<tr>
<td>Flumadine</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td>Halothane</td>
<td>Rimipinoid</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Sulphonamide</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tetrabamantone</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>Tolcapone</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Zoxazolamine</td>
</tr>
</tbody>
</table>

**Tab. 29.3:** Some medicaments that may provoke idiosyncratic fulminant or protracted liver failure in isolated cases (s. tab. 29.9)

The initial diagnosis is based mainly on the determination of laboratory values, which can be used as starting values in order to assess the further course of disease. (s. tab. 29.4) • The same applies to sonography as regards the determination of liver size and echo structure. (Liver size can also be determined exactly by means of CT.)

GC protein (group-specific component) is an α1-globulin which is synthesized in the liver and which binds actin released due to hepatocyte decay. Decreased GC-protein values in the plasma are thus attributable both to its reduced synthesis in acute liver failure and its increased binding to actin as a result of hepatocellular disintegration. A value of <34 μg/ml was associated with a lethal outcome in some 70% of cases.

The mortality rate depends on the cause of disease, the patient’s age as well as the intensity and duration of encephalopathy. Since the introduction of liver transplantation and temporary liver-supporting systems, the mortality rate in acute liver failure has been reduced markedly. (41)
Chapter 29

Basic diagnostics:  Coagulation:
haemogram  Quick’s value
urinalysis  T-AT-III complex
electrolytes  factor V
glucose  glucose
blood gas analysis  blood gas analysis
LDH  LDH
Liver:  Kidney:
GPT, GOT, GDH  urea
bilirubin  creatinine
cholinesterase  cholinesterase
GC protein  GC protein

Sonography  CT

Tab. 29.4: Diagnostic measures in suspected fulminant liver failure

5 Clinical aspects

Liver damage caused by drug-induced toxicity, more specifically the intrahepatic obstructive type of jaundice resulting from the intake of arsphenamine, was first described by F. M. Hanger et al. in 1940. (36)

5.1 Clinical courses

Toxic liver damage does not produce a characteristic clinical picture. It is determined by the underlying lesion pattern. Clinical courses range from asymptomatic to symptomatic and from acute to chronic. (1, 2, 4, 10, 16, 18, 30, 32, 40, 44–47, 49, 52, 59, 62, 64, 69, 73, 74, 80–83, 86, 88, 89, 91, 93, 95, 97, 100)

Drug-related hepatic damage can mimic almost any liver disease and must, therefore, always be included in the differential diagnosis. (s. tab. 29.5) • Thus, a pure jaundice type may occur with only unconjugated hyperbilirubinemia, or a cholestasis type is witnessed, which may or may not be accompanied by simultaneous jaundice. (s. figs. 29.3, 29.4) The fatty liver type may start out uneventfully with no abnormal laboratory values until increased levels of γ-GT and, in several cases, an additional rise in GPT and ChE occur. The hepatitis type with greatly varying laboratory values also produces a clinical picture with multiple interpretations: it may present as acute hepatitis, protracted or persistent hepatitis, unspecific reactive hepatitis, or “granulomatous” hepatitis. The liver damage may progress as a cholestatic hepatitis type, necrotic type (s. fig. 29.2) or cholangitis type (s. fig. 29.5), with the corresponding suggestive laboratory findings. • Chronic courses of liver disease include chronic active hepatitis, cirrhosis, fibrosis, or vascular type and tumour type. • Combined forms of damage are also frequent. Their diagnostic categorization presents considerable difficulties. (s. tab. 29.9)

5.2 Anamnesis

Anamnesis of the damage may show, if at all, atypical complaints, which could, however, be suggestive of toxic liver damage:

<table>
<thead>
<tr>
<th>Pruritus</th>
<th>Lack of appetite</th>
<th>Lacrimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Nausea</td>
<td>Common cold</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.3 Findings

The following clinical findings can be considered as additional symptoms for the detection of liver damage caused by drug-induced toxicity:

<table>
<thead>
<tr>
<th>Abdominal pain</th>
<th>Rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Exanthema</td>
<td>Eosinophilia</td>
</tr>
<tr>
<td>Scratching</td>
<td>Leucocytosis/leucopenia</td>
</tr>
</tbody>
</table>

5.4 Laboratory findings

The focus is on determining γ-GT as an indicator of long-term (several weeks) strong induction of the biotransformation system as a result of drug intake – once other causes of elevated γ-GT have been excluded. (s. p. 85) Generally, the γ-GT level remains normal only during intake of oral contraceptives or long-term contact with halothane (values are even subnormal in patients taking oestrogen). • A rise in GPT (generally also in GOT) suggests the development of drug-induced hepatocellular damage. Generally, a so-called inflammatory type (DeRitis quotient < 1) can be identified. (s. p. 83) In this context, γ-GT is therefore regarded as the screening enzyme for drug-related induction of the biotransformation system, and GPT is seen as the screening enzyme for the resulting hepatocellular damage. • Decreased levels of cholinesterase point to a reduction in ChE synthesis in the area of the rough endoplasmic reticulum due to drug-related toxicity. Intake of hormone-based contraceptives likewise culminates in diminished ChE activity. (s. p. 90) • The increase in AP suggests a toxic hepatic lesion of the cholestatic type
Drug-induced liver damage

(with or without jaundice), possibly with simultaneously augmented or normal GPT (and GOT). (s. p. 89) • This so-called threefold pattern ($\gamma$-GT, GPT, ChE) is regarded as an efficient and rational test to demonstrate hepatic damage with a sensitivity of approx. 95%. Cholestasis is detected by the fourfold pattern ($\gamma$-GT, GPT, ChE, AP) with a sensitivity of approx. 96%. (s. p. 91) (s. tab. 5.11) Additional diagnostic findings can be generated from the enzyme ratios. (s. p. 83) (s. tabs. 5.6, 5.7) (s. tabs. 29.4, 29.5)

1. Jaundice type
   - bilirubin ↑
2. Cholestasis type
   - AP, LAP, $\gamma$-GT ↑
3. Jaundice-cholestasis type
   - bilirubin, AP, LAP, $\gamma$-GT ↑
4. Fatty liver type
   - $\gamma$-GT ↑, perhaps GPT, ChE ↑
5. Hepatitis type
   - GPT, GOT, GDH, $\gamma$-GT ↑
   - DeRitis quotient < 1
   - generally bilirubin, AP, $\gamma$-GT ↑; ChE, Quick ↓
6. Cholestatic hepatitis type
   - GPT, GOT, GDH, $\gamma$-GT, AP ↑
7. Necrosis type
   - GPT, GOT, GDH ↑
   - DeRitis quotient > 1
   - generally bilirubin, AP, $\gamma$-GT ↑; ChE, Quick ↓ possibly bilirubin, $\gamma$-GT, GPT, ChE ↓ possibly autoantibodies +
8. Cholangitis type
   - GPT, GOT, GDH, $\gamma$-GT, AP ↑
   - possibly bilirubin ↑, ChE ↓ possibly autoantibodies +
9. Chronic hepatitis type
10. Cirrhosis type
11. Fibrosis type
12. Vascular type
13. Tumour type
14. Combined type

Tab. 29.5: Morphological reactions or laboratory findings resulting from hepatic damage caused by medicament-induced toxicity (s. tab. 29.9)

Evidence of autoantibodies, such as ANA, AMA, SMA, points to the immuno-allergic pathogenesis of medicament-induced liver damage. These autoantibodies can be detected both singly and in a combined form. Usually, they occur in low titres. As a rule, they have been found with clometazine, fenofibrate, oxyphenisatine, papaverine, etc. Anti-LKM 2 was detected after taking ticrynafen, and anti-LM after dihydralazine. (The subgroup AMA anti-M$_6$ has been identified as a specific antibody following the intake of iproniazid; it has not been found since iproniazid was taken off the market). However, autoantibodies are of no diagnostic value in medication-induced liver damage.

5.5 Search for causes

In most cases, the search for the causal toxin must be carried out with detective-like meticulousness. However, neither in the physician’s practice nor in hospital can this search be conducted with the required precision, because the time available is not sufficient to establish the individual medication history in depth, or the patient is generally agitated and cannot answer detailed and direct questions satisfactorily. Drug- and/or chemical-related anamneses are often incomplete or unreliable, because the patient was not given sufficient time at the doctor’s surgery and was not able to take a close look at the medicines stock at home in order to provide more precise answers. • For these reasons, our checklist, given to the patient in the form of a questionnaire, has proved to be of great assistance over many years. (s. tab. 29.6)

Intake via:
- Skin
- Mouth
- Inhalation
- Blood vessels

Since when? Until when?
How much? How often?

1. Medication?
2. Hormones? (oral contraceptive, etc.)
3. Chemicals? (job, hobby, home, garden, environment)
4. Alcohol?
5. Drug abuse?
6. Cosmetics? (after-shave? personal hygiene products?)
7. Tonics?
8. Aphrodisiacs? (potency drugs)
9. Mixed-herbal teas?
10. Food preservatives? Special foodstuffs?
11. Body contact with chemicals? Synthetics?
12. Journeys abroad?

Tab. 29.6: Check-list for the detection of possible hepatotoxic xenobiotics

Very few terms in this questionnaire require further explanation, and we also include some brief instructions about how to answer the questions. The patient has sufficient time to think about the individual questions either at home or in hospital, is able to consult family members and may even take several days to complete the questionnaire. While discussing the responses with the doctor, further information can be added. This may require repeated and sometimes outright “inquisitory questioning”, as the patient (1.) may have forgotten to mention certain medicaments or may not consider them as such (e.g. laxatives). (2.) may be ashamed to admit taking or abusing certain agents (e.g. aphrodisiacs – sometimes of rather obscure composition), (3.) may fear
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History, Morphology, Biochemistry, Diagnostics, Clinic, Therapy
Kuntz, E.; Kuntz, H.-D.
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